

The extensive contribution of Dionisio Nieto and Alfonso Escobar to Minckler's treatise on neuropathology

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ABSTRACT

Dr Dionisio Nieto received excellent training in neurology, psychiatry, and neuropathology from masters in both Spain (Sanchís Banús, Del Río Hortega) and Germany (Spielmeyer, Bumke, Bonhoeffer, and Kretschmer). He had a calling to continue and expand the brilliant trajectory of these disciplines in the first decades of the 20th century in Spain. Unfortunately, this valuable progress was stopped dead by the Spanish Civil War, which forced many leading figures into exile; this group included Nieto, who emigrated to Mexico, creating his own school there. One of his main disciples was Dr Alfonso Escobar. Together, they developed a significant scientific career that afforded them great prestige in the international neuropathological community. As a result of this status, they were charged with writing six chapters for the first great English-language treatise on neuropathology, edited by Jeff Minckler.

This study presents a detailed review of those six chapters. The review identifies the authors' mastery of neuropathological technique, their great expertise, and the originality of some of their contributions. Specifically, Nieto and Escobar were pioneers in describing secondary degeneration of limbic structures connected to the sclerotic hippocampus in patients with temporal lobe epilepsy, a finding that has been rediscovered thanks to magnetic resonance imaging. Furthermore, using an original method, they observed diffuse gliosis in the midbrain/diencephalon of patients with schizophrenia; this finding has not been confirmed in subsequent studies, perhaps due to methodological differences. The other four chapters address neurosyphilis, nervous system parasitic diseases, stress, and basic histological staining techniques.

KEYWORDS

Epilepsy, Escobar, Minckler, neuropathology, Nieto, schizophrenia

Introduction

Among the many devastating consequences of the Spanish Civil War of 1936-1939, neuroscience suffered the exile of many of its leading figures, thanks to whom Spain was, at the time, at the forefront of the field internationally. Under the colossal shadow of Cajal, and with the assistance of the Junta para la Ampliación de Estudios (Board for Study Extensions) and other institutions, new generations of researchers had been able to undertake training at Europe's finest centres, subsequently

returning to Spain to contribute to the great developments in neurology, psychiatry, neuropathology, and neurohistology. All this progress was lost with the war and the foreign or domestic exile of leading figures in neuroscience, as well as the early death of Achúcarro and the death of Cajal.

One of these young talents (aged 31 years in 1939) was Dionisio Nieto, who had received excellent training; Nieto's life and work are addressed in a definitive article by Giménez Roldán.¹ He is also mentioned by Dosil² in a

study recalling the group of distinguished Spanish neuroscientists who left a mark on Mexico during their exile. Rahmani et al.³ published a worthy review of Nieto's life and scientific work, which is also analysed in the doctoral thesis of Nieto's daughter Adela.⁴ García-Albea⁵ and Escobar⁶ (the latter was Nieto's main disciple) also reviewed his scientific oeuvre. The review by García-Albea⁵ is particularly complete. He calculates Nieto's total scientific output at 115 published works, categorising them as follows: anatomical basis of mental illness; cerebral cysticercosis; laboratory; pure neurology; neurology and psychiatry as disciplines; psychopharmacology; experimental neurology and psychiatry; and history.

This article is not intended as another review of Nieto's professional and scientific career, but rather focuses on his extraordinary contribution, in collaboration with Escobar, to Minckler's⁷ treatise on neuropathology, which is an excellent reflection of Nieto's great prestige in the international neuropathological community.

In his foreword to the treatise, Arthur Weil explains how the German literature had dominated the field of neuropathology throughout the 20th century. He notes that the still weak American neuropathology, cultivated by a handful of dedicated researchers in the first decades of the 20th century, had had to make do with the relatively modest works of a single author as its main sources of information.⁸⁻¹⁰ Indeed, it was not until 1958 that the first English-language treatise with multiple authors was published; this work was edited by Greenfield,¹¹ and was a great success, with numerous new editions appearing over the years. Around the same time, two short introductory works on neuropathology were published, one in English, by Adams and Sidman,¹² and one in French, by Escourolle and Poirier¹³; both enjoyed great popularity. However, there was no great neuropathological treatise in the English language.

This was clear to Weil, who noted that this important need remained unmet in the 1960s. He lamented the lack of an English-language neuropathology *Handbuch*, at a time when the specialty was fairly well developed in the United States, partly due to the immigration of numerous researchers from Germany and other countries, fleeing the Nazi regime. As an example of this development, we may cite Harry Zimmerman,¹⁴ one of the fathers of American neuropathology, who had studied with Spielmeyer in Munich in 1929. By the 1960s, the Montefiore Hospital in New York had already become

the home of a consolidated neuropathology laboratory that trained a considerable proportion of neuropathologists from the United States and abroad.

The term handbook is one of the most inappropriate German loanwords used in English: rather than a manual or pocket book, the German *Handbuch* refers to a large treatise with multiple authors, published in numerous thick volumes. The German tradition is very rich in *Handbücher*, both on general medicine and on neurology and psychiatry. As examples related to neuropathology, Weil cites *Handbuch der Geisteskrankheiten*, whose Volume VII, spanning 1130 pages, was edited by Spielmeyer in 1930, and the *Handbuch der speziellen pathologischen Anatomie und Histologie* (published between 1955 and 1958), whose Volume XIII (entitled *Nervensystem*), over 9000 pages long, was edited by W. Scholz.

The only precedent of an English-language neuropathological textbook with multiple authors was that edited by Penfield¹⁵ in 1932, with contributions from Pío del Río Hortega and Fernando de Castro. The first two volumes of the textbook focused on the cytology and histology of the nervous system, and the third addressed only the neuropathology of brain tumours, without addressing the remaining neurological diseases; therefore, it cannot truly be considered a neuropathology treatise.

Thus, Weil finally concludes that the *raison d'être* for an "encycopedic Neuropathology in the English language" is well founded. The editorial work was the responsibility of Jeff Minckler,⁷ who, in his extensive preface to the work, explained the methodology he had followed to coordinate 163 authors from 23 countries over a period of 5 years. This extended time period, during which several contributors died, forced him to make constant updates and revisions in the complex editorial process. He had initially planned to publish the work in two volumes, but eventually expanded it to three due to the length of the various chapters. This third volume includes the chapters by Nieto and Escobar, which are reviewed in this article.

Material and methods

The information for the brief biographies is taken from the aforementioned references on Nieto,¹⁻⁶ and two additional sources on Escobar.^{16,17} Together, the authors wrote a total of six chapters¹⁸⁻²³ for Minckler's treatise; the book is available online, enabling consultation and

review of all these chapters for their analysis and evaluation in the context of the international neuropathology of the day. Escobar⁶ himself also wrote a brief evaluation of each of the chapters.

Results

Brief biography of Dionisio Nieto¹⁻⁶

Nieto was born in Madrid in 1908, where he studied medicine from 1923 to 1929. His doctoral thesis (1934) was entitled “Contribución al estudio clínico e histopatología del sistema nervioso central en la psicosis pelagrosa” (Contribution on the clinical study and histopathology of the central nervous system in pellagrous psychosis).^{1,5} His main masters were Sanchís Banús, of the psychiatry department of Hospital Provincial de Madrid, and Pío del Río Hortega, at the Laboratory of Normal and Pathological Histology. With a grant from the Junta para la Ampliación de Estudios, he was able to move to Germany, where he studied for nearly three years under Spielmeyer, Bumke, Bonhoeffer, and Kretschmer. Upon his return to Spain, he once more joined the Hospital Provincial, as well as the Cajal Institute, directed by Rodríguez Lafora. With the outbreak of the Spanish Civil War, he was appointed director of the Ciempozuelos psychiatric hospital, but was later dismissed by the Francoist authorities, who appointed Vallejo-Nájera as his replacement. With the end of the war, he took exile, first in Paris and Bordeaux and then, from 1940, in Mexico. His first professional role there was at the vast mental asylum of La Castañeda, where he initially joined the anatomical pathology division, subsequently becoming a resident physician. After the closure of that antiquated centre, the National Institute of Neurology and Neurosurgery was created, with Nieto leading the psychiatry and brain research division from 1964. He also played a role in the founding of the Laboratory of Medical and Biological Studies (later renamed the Institute of Biomedical Research). This endeavour was supported by the House of Spain and the Universidad Autónoma de México, with financial assistance from the Rockefeller Foundation. He was chair of Nervous System Pathology at the Universidad Autónoma de México. He did not return to Spain until 1977. Later, he made various trips, including one to receive the gold medal of the Universidad Complutense de Madrid. Nieto was married to Catalina Vallejo, with whom he had three children, Felipe, Victoria, and Adela. He died in January 1985.

Brief biography of Alfonso Escobar^{16,17}

Escobar was born in 1929 in Cunduacán (Mexico), but his family moved to Veracruz shortly thereafter. He studied medicine at the Universidad Autónoma de México. In 1944, he contacted the Laboratory of Medical and Biological Studies, where he met Dr Nieto. In 1956, he joined the laboratory as a researcher. He was appointed head of neuropathology at the National Institute of Neurology and Neurosurgery. In addition to his considerable work on clinical diagnosis, he performed numerous experimental studies on toxic pathologies and deficiency diseases of the nervous system, on models of epileptogenesis, on the effects of stress or dietary deficiencies on neurodevelopment, hormonal influences on global brain ischaemia, etc; in total, he published over 250 articles. He enjoyed international recognition, and sat on the editorial boards of such prestigious journals as *Brain Pathology*, *Experimental Neurology*, *International Journal of Neuroscience*, and *Journal of Neuropathology*. He was invited as a guest lecturer to numerous universities in the United States, Iran, and Europe. He was recognised as an emeritus professor and researcher, and received several of Mexico's most prestigious awards, including the Doctor Ramón de la Fuente Muñiz award for mental health, presented by the country's president. A great tribute to him was organised for the occasion of the 60th anniversary of his professional activity, at his beloved Institute of Biomedical Research, where a lecture hall was named after him. He died on 14 October 2020, surrounded by his family.

The chapters in Minckler's treatise

1. Neurosyphilis¹⁸

This extensive chapter, with Escobar signing as first author, spans 17 pages (plus references), and contains 27 micro- and macroscopic figures. It follows a classical structure: general paralysis of the insane (GPI), tabes dorsalis, other myelopathies, peripheral nervous system lesions, meningovascular syphilis, hypertrophic pachymeningitis, cerebrovascular syphilis, and gummata. It constitutes a small but complete treatise on the neuropathology of neurosyphilis. It is worth mentioning the variety of histological stains used in the microscopic figures, demonstrating Nieto's great technical ability, the fruit of his training in the Spanish school of histology as well as his own methodological genius: two of the stains

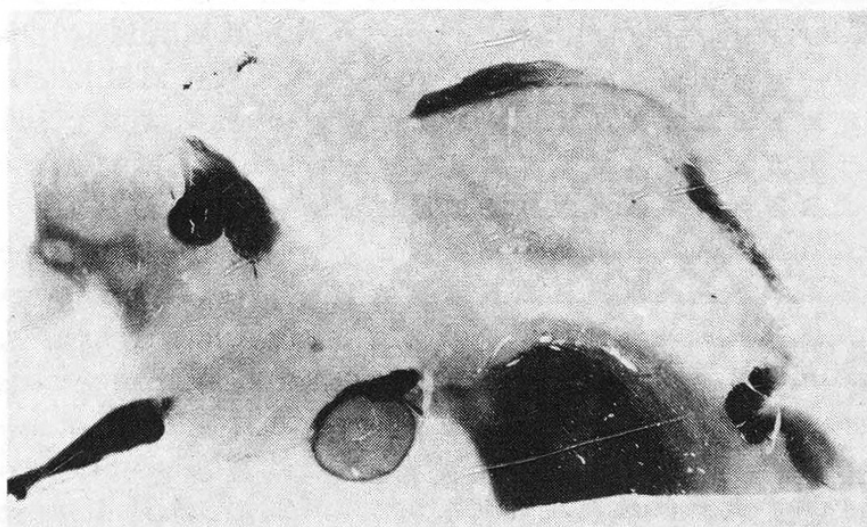


Fig. 177-4. Sagittal section of same specimen that shows marked demyelination especially in thalamic nuclei. Nieto's method for myelin.

Figure 1. Sagittal section of the diencephalon, stained with Nieto's myelin technique. Demyelination of the thalamus and hypothalamus of a patient with general paralysis of the insane. Source: Escobar A, Nieto D. *Neurosyphilis*. In: Minckler J, ed. *Pathology of the nervous system*. New York: McGraw-Hill; 1972.

used, one for myelin (Figure 1) and one for spirochaetes, were of his own invention. Nieto and Escobar also used the haematein-eosin, Nissl, Holzer, Cajal gold-sublimate, Hortega (silver), Turnbull (iron), haematoxylin-Van Gieson, and Klüber Barrera (mixed myelin/neuronal) staining methods.

The authors acknowledge that at the time of writing, neurosyphilis was not as relevant as it previously had been, having been associated with the history and leading figures of neuropathology itself. Neurosyphilis research made great contributions to the field of psychiatry, as well as neurology, with the identification of sensory pathways in the spinal cord, for example. It had also generated important neuropathological contributions, such as the trans-synaptic degeneration of the lateral geniculate nucleus, secondary to degeneration of the reticulogeniculate tract. Among the historic contributions, they highlight those of Alzheimer and Nissl, who had definitively demonstrated that GPI was essentially a chronic encephalitis.

In the macroscopic findings section, they highlight leptomeningeal thickening and adherences and the potential presence of subdural haemorrhage. In the brain parenchyma, the authors note gyral atrophy and granulations on the ependymal wall of the ventricles. Dilation of the third ventricle is explained by atrophy and demyelination of the thalamus and hypothalamus, as the authors demonstrate using the Nieto myelin staining technique (Figure 1). The authors describe a simple yet ingenious manoeuvre that may be used to detect "dementia paralytica iron," a ferrous deposit on the cortical surface that, though non-specific, is highly characteristic of GPI. They use specific Turnbull staining to histologically demonstrate the presence of this perivascular iron deposition.

In the microscopic findings section, they describe and illustrate all the classical signs: 1) perivascular inflammatory cell infiltration, mainly composed of plasma cells; 2) the great (in their words, "kaleidoscopic") variety of pictures of neuronal degeneration, preventing them from

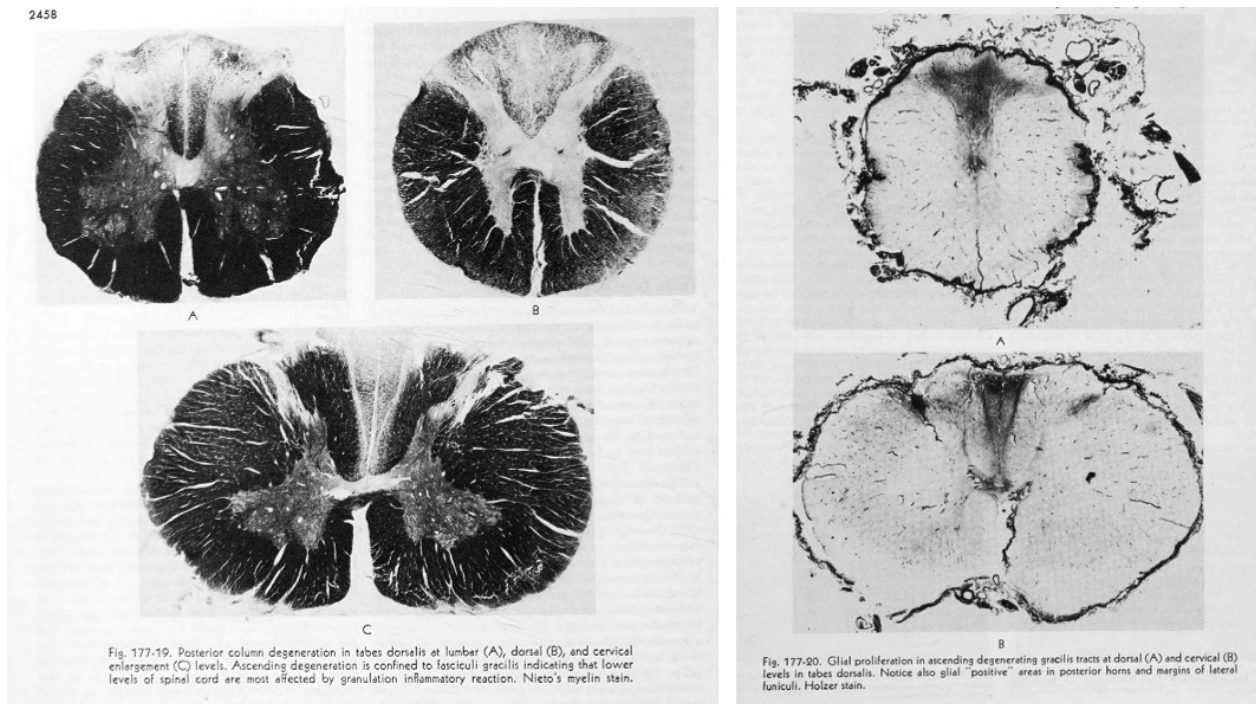


Figure 2. Transversal section from the spinal cord of a patient with tabes dorsalis. Left: Nieto's myelin staining method demonstrates demyelination of the posterior columns, with predominant involvement of the fasciculus gracilis. Right: Holzer staining demonstrates gliosis of the same posterior columns. Source: Escobar A, Nieto D. Neurosyphilis. In: Minckler J, ed. Pathology of the nervous system. New York: McGraw-Hill; 1972.

identifying any one sign as being more or less specific to GPI; 3) marked glial proliferation, both in terms of the number and the hypertrophy of cells; and 4) the abundance of Hortega rod-like cells, particularly in early stages, and the reduction in their number with treatment.

The section dedicated to GPI concludes with a review of its different "forms," including the galloping, latent, and juvenile forms (secondary to congenital syphilis). The latter form displays marked cerebellar involvement. They also describe the senile form and Lissauer's paralysis, characterised by more focal lesion distribution, more posterior involvement, and greater presence of epileptic seizures.

Regarding tabes dorsalis, the authors review the classical descriptions, highlighting the fundamental point that despite significant radicular and posterior column degeneration (Figure 2), the number of neurons in the spinal ganglia is not greatly reduced (and may be normal).

Thus, they insist on the possible pathogenic relevance of meningeal thickening, strangling the fibres of the posterior columns at the point of entry into the spinal cord, as a pathogenic mechanism in the ascending posterior radiculo-cordonal degeneration. To support this hypothesis, they contribute a curious argument about the presence of spirochaetes in the lumbar cerebrospinal fluid (CSF).

Drawing on their significant experience, Escobar and Nieto unequivocally express their scepticism regarding the so-called "syphilitic amyotrophy" defended by Dejerine himself. Their opinion is based on the fact that they had never observed significant inflammatory or degenerative involvement of motor neurons in the anterior horn of the lumbar spinal cord.

The authors dedicate considerable space to a discussion of the frequency and presentation of optic atrophy in neurosyphilis. They considered that optic atrophy in GPI may be more frequent than was believed, but that it could

not be easily detected in vivo due to the patients' mental conditions. In *tabes dorsalis*, the frequency of optic atrophy was thought to be very high and, in the authors' opinion, clearly related to meningeal thickening and inflammation (they present a figure [177-24] that perfectly illustrates this). Furthermore, this optic nerve lesion was accompanied by atrophy of the retina and trans-synaptic degeneration of the lateral geniculate body.

In the section on meningovascular syphilis, the authors argue that, initially, meningitis predominantly affects the base of the brain and is of low intensity; subsequently, it may progress to more severe forms with cranial nerve involvement, extension to the parenchyma, vascular alterations, and spinal involvement. The most severe form was *pachymeningitis cervicalis hypertrophica*, in which the meninges formed a "tube" compressing the spinal cord, which nonetheless presented minimal extension into the cranial cavity.

They thoroughly describe Heubner arteritis, which presents inflammatory infiltration of the adventitia, fibrous degeneration of the tunica intima, intense breaking-up of the elastic membrane, and endothelial proliferation. What begins as periarteritis progresses to panarteritis, leading to ischaemia and possible haemorrhage. Once more, with the authority of their great experience, the authors felt able to question the existence as an independent entity of the variety of exclusively small-vessel disease described by Alzheimer and Nissl.

Finally, Nieto and Escobar address cerebral gumma, of which they had observed several cases presenting with one or more gummata. They give a detailed description of the histological characteristics of cerebral gummata, concluding that they are essentially granulomas similar to those observed in tuberculosis.

2. Parasitic diseases¹⁹

As in the previous chapter, Escobar is listed as the first author. This chapter is also very extensive, with 17 pages plus 90 bibliographical references. As we may expect, a significant part of it is dedicated to cysticercosis, a disease that was (and still is) endemic in Mexico. However, the authors also address in detail amoebiasis and malaria, with shorter sections addressing coenurosis, echinococcosis, schistosomiasis, paragonimiasis, filariasis, angiostrongyliasis, *Toxocara canis* encephalitis, and gnathostomiasis, on which we will not comment in this article. They do not include toxoplasmosis, which is addressed

in a separate chapter.

Beginning with amoebiasis, the authors note that cerebral abscesses are rare in this disease. They distinguish between two basic forms of cerebral invasion. The first is the acute, very severe variety of primary meningoencephalitis without involvement of other organs. This form is caused by free-living amoebae in water. The disease most frequently affects children and young adults, who contract the infection by swimming in contaminated water, with the parasite entering the body through the nose and reaching the brain via the olfactory tract. The other variety is a late complication in the progression of amoebiasis, and consists in haematogenous dissemination of abscesses from other parenchymal foci, particularly the intestine, liver, or lungs.

In malaria, cerebral invasion is observed with *Plasmodium falciparum* infection, and occurs in both acute and chronic forms of the disease. There are two main types of brain lesions: the grey matter displays granulomas, whereas the white matter presents multiple petechial lesions (a "brain purpura") corresponding histologically to "ring haemorrhages," with capillaries "engorged with erythrocytes."

Regarding cysticercosis, the authors first review the parasite's life cycle and pathways of infection. Among these, they contribute a novel observation of Nieto's: intrauterine infection of a fetus whose mother died due to neurocysticercosis. They list the different locations of cysts (parenchymal, intraventricular, subarachnoid, or racemose), with some patients presenting combinations of the different locations. They highlight the miliary form, presenting with a multitude of small cortical cysts, which is more commonly observed in children. The authors present a brief review of the clinical manifestations of cysticercosis, based on Nieto's extensive experience, with 168 previously published cases. They also review the CSF alterations observed, particularly eosinophilia, which is more frequent in meningeal and ventricular cysts and less common in intraparenchymal cysts, in which the diagnostic value of CSF analysis is low. They note that racemose forms present basal inflammation or meningitis, with a possibility of secondary vascular lesions. They give a perfect description of the different phases of progression of cysts, from the initial phases, in which they contain a clear fluid and viable parasite, to grumose degeneration and finally calcified fibrosis. They also describe in detail the structure of the parasite and how to

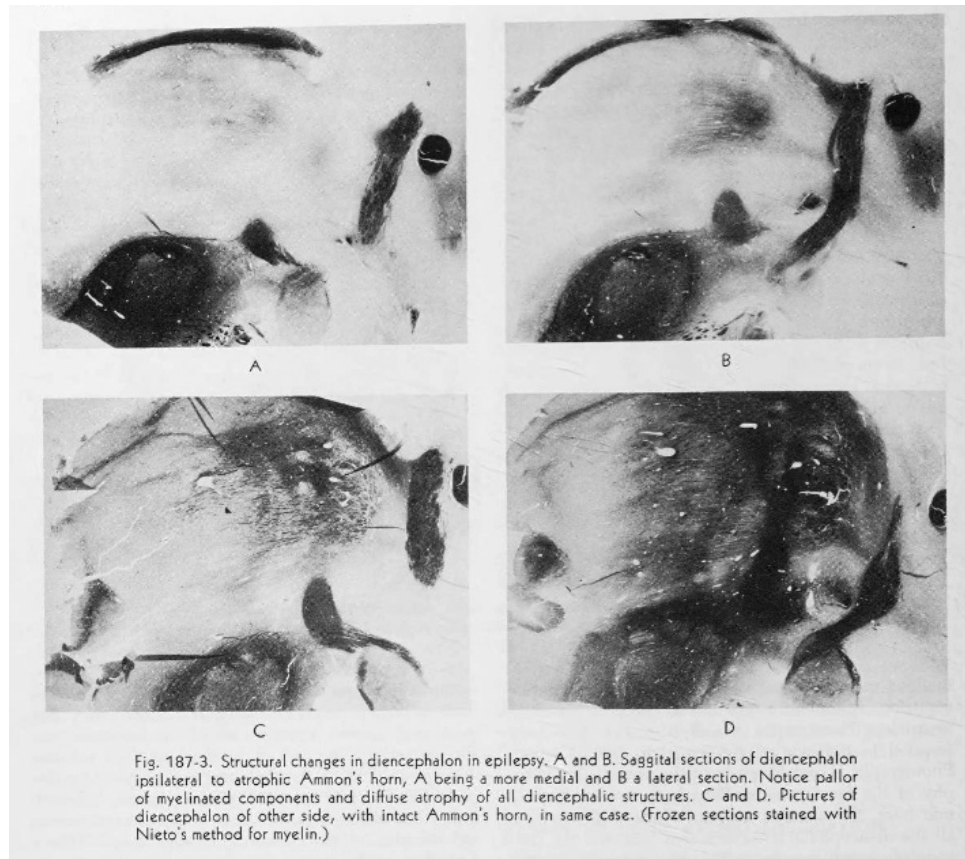


Figure 3. Sagittal section of the diencephalon, stained with Nieto's myelin technique. Above: both images demonstrate thalamic demyelination ipsilateral to hippocampal sclerosis. Below: normal myelination in the contralateral thalamus. Source: Escobar A, Nieto D. Neurosyphilis. In: Minckler J, ed. Pathology of the nervous system. New York: McGraw-Hill; 1972.

identify it in fresh samples by placing a cyst between two slides and observing the crown of suckers and hooklets around the scolex.

3. Epilepsy²⁰

This chapter lists Nieto as the first author. He begins by commenting on the limited attention placed on epilepsy, both in neuropathology texts and in neurology and psychiatry works.

From the beginning, he distinguishes between two main forms: idiopathic epilepsy and symptomatic epilepsy, secondary to a wide variety of cerebral lesions, which the article does not further address. Gastaut is cited as an authority, with a quote highlighting the lack of understanding of the neuropathology of idiopathic epilepsy.

The chapter summarises the history of the discovery of hippocampal sclerosis (Ammon's horn), and especially Sommer's contribution on the particular vulnerability of the sector of the pyramidal cell layer that bears his eponym (today, area CA1), which shows predominant neuronal loss.

The authors note that Alzheimer had previously established that 50%-60% of the brains of patients with "genuine epilepsy" presented hippocampal sclerosis, as well as marginal cortical gliosis, which Alzheimer associated with dementia. Nieto was surprised that no previous author had described the degenerative lesions that, according to neuropathological logic, must occur in the anatomical projections of the affected Ammon's horn. Regarding the latter point, he cites his own work,

having described these secondary degenerative lesions in a Mexican journal. These lesions include atrophy of the fornix, mammillary body, mamillothalamic tract, anterior nucleus of the thalamus, and other structures surrounding the third ventricle. Using his own myelin staining method, he describes demyelination of thalamic and hypothalamic nuclei. With Hortege's method, he demonstrates gliosis of the anterior and medial dorsal nuclei of the thalamus (Figure 3). After a pertinent discussion, he concludes that these are not secondary lesions, but rather are concomitant with sclerosis of Ammon's horn. Fittingly, he cites Spielmeyer, who had observed hippocampal sclerosis in patients with epilepsy secondary to other causes. This leads Nieto to consider that hippocampal sclerosis may be secondary to anoxia or ischaemia.

In this regard, he fully subscribes to the hypothesis of Penfield, previously posited by Etinger and Meyer, that hippocampal sclerosis is secondary to compression of the brain during childbirth. However, he acknowledges that it may be caused by other cerebral insults during early childhood.

He unequivocally asserts that hippocampal sclerosis is the most epileptogenic of brain lesions, and that this lesion is related to seizures with psychic semiology and with idiopathic epilepsy.

He identifies two unresolved questions. Firstly, the delay between the brain lesion occurring during birth and seizure onset, years later. Secondly, he considers the fact that hippocampal sclerosis is also observed in brains of individuals who never had epilepsy. Regarding the first point, he notes cases of other diseases presenting with delayed onset after the brain injury, for example parkinsonism secondary to encephalitis or carbon monoxide poisoning. Regarding the second question, he suggests that a possible explanation may be genetic predisposition and the presence of other associated lesions. He summarises this with a curious formula in which epilepsy is the sum of four possible factors: $\text{epilepsy} = \text{HP} + \text{AL} + \text{DL} + \text{OCL}$ (HP: hereditary predisposition; AL: Ammon's horn lesion; DL: diencephalic lesion; OCL: other cerebral lesions).

4. Major psychoses²¹

This chapter also lists Nieto as the first author. He considers two main types of major psychosis: schizophrenia and manic-depressive psychosis, in the terminology used at

the time. Curiously, in addition to this chapter by Nieto and Escobar, Minckler also commissioned Roizin²⁴ to write another chapter specifically addressing schizophrenia; this is beyond the scope of the present study. Nieto recalls the classic dichotomy: some psychoses, such as schizophrenia and manic-depressive psychosis, progress without demonstrated neuropathological lesions, whereas other cases present clear brain lesions; these are the organic psychoses. With a single sentence, he dismisses as an oversimplification the notion that functional psychoses might be of purely psychic origin on account of the lack of a demonstrable neuropathological lesion. The lack of a demonstrated anatomical substrate may simply be due to the low sensitivity of the available techniques, which could be overcome by advances in neurochemistry or histology. In any case, he asserts that the lack of a clear neuropathological alteration in manic-depressive psychosis did not surprise him, due to the clear genetic component in its causation.

Regarding schizophrenia, he begins by reviewing classic authors (Alzheimer, Kraepelin, and many others), concluding that their neuropathological findings were non-specific. The article subsequently reviews more recent or contemporary literature, which also reported contradictory results.

Nieto then presents in detail his own studies, which had been communicated previously ("Cerebral lesions in schizophrenia. Their neuroanatomical and neurophysiological significance," Second International Congress for Psychiatry; Zurich, 1957). Given the limited success of other authors who had focused their research on the cerebral cortex, he chose to study in detail the diencephalon and midbrain. Furthermore, considering the difficulty of estimating neuron density in the different nuclei of these structures, he opted to focus his work on studying the glia. This decision was based on the well-established notion that all neuronal loss is accompanied by gliosis, which is easier to observe than the number of neurons. Nieto recalls that the traditional means of highlighting gliosis was Holzer's method, which selectively stains neuroglial fibrils; however, he dismisses this technique due to its lack of consistency. Thus, he opts to use the lithium-silver carbonate method developed by his master Del Río Hortege. The main advantage of this technique is that it stains the entire glial cell, not just the fibrils. However, the method does present some challenges, and is very difficult to follow for those who have not mastered it. Firstly, specimens must be fixed in

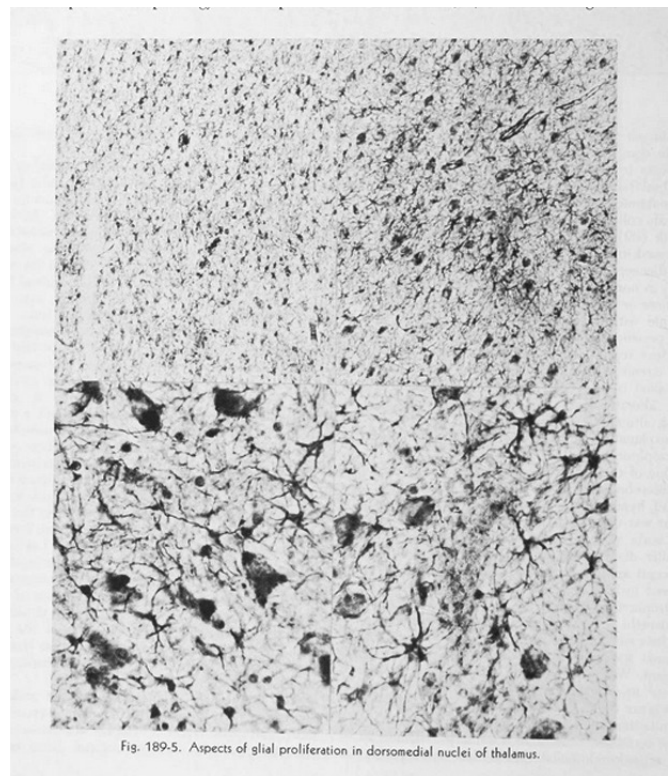
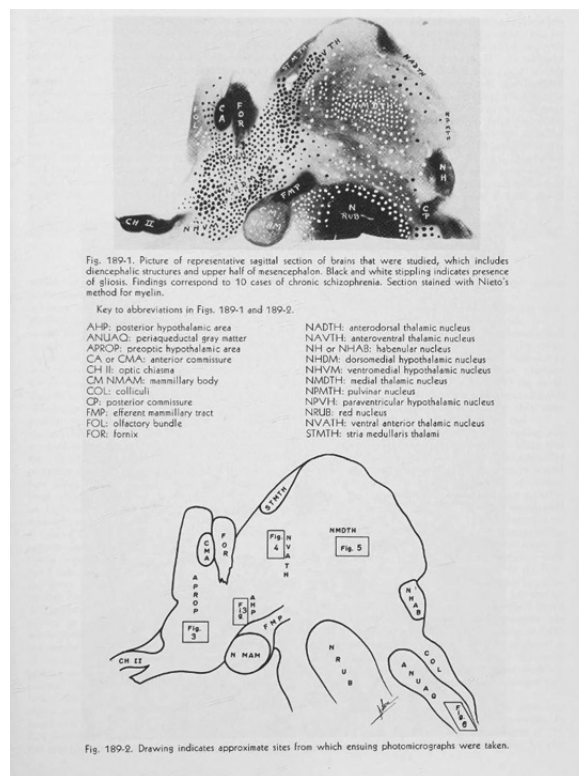


Figure 4. Two figures from the chapters on the neuropathology of psychoses. Top left: sagittal section of the diencephalon, stained with Del Río Hortega's lithium carbonate/silver nitrate technique; stippling by Dr Nieto indicates the presence of gliosis. Bottom left: diagram showing the approximate locations of the photomicrographs reproduced in the following figures. Right: gliosis of the medial dorsal nucleus of the thalamus, at three increasing levels of magnification. Source: Nieto D, Escobar A. Major psychoses. In: Minckler J, ed. Pathology of the nervous system. New York: McGraw-Hill; 1972.

Cajal's formalin bromide, as the method fails if formalin is used for fixation. Furthermore, sections must be made with frozen tissue; this requires much greater technical skill than slicing of paraffin-embedded specimens.

Observing all these methodological requirements, Nieto studied 10 brains of patients with chronic schizophrenia, comparing them with the brains of 3 controls. The main finding in all patients was diffuse gliosis of the reticular formation of the midbrain, hypothalamus, anterior and medial dorsal nuclei of the thalamus, and the periaqueductal grey matter (Figure 4). Nieto highlights how, in line with the initial hypothesis, the study of neurons in these structures using Nissl staining was non-contributory. As

a relevant additional finding, he notes that four patients presented Ammon's horn lesions, but without secondary degeneration of anatomically connected structures.

He openly wonders about the meaning of these findings and whether they may be the cause or the consequence of schizophrenia. He considers the possibility that they have no great relevance, but concludes that they are related to the disease and signals the need for further study with larger numbers of cases and using different diseases as controls. He also considers that the damaged structures, which are part of the Papez circuit and essential in psychic life, show a clear relation to the symptoms of schizophrenia.

5. Stress²²

This chapter, whose subject is at once generic and very specific, lists Escobar, who had dedicated other works to the subject, as the first author.

As a starting point, the authors consider the principle of psychosomatic medicine, according to which both physical and mental stress may cause tissue alterations in all the organs of the body. They point out the resistance of nervous tissue and its tendency to remain intact. However, they acknowledge the changes that may be observed in neurons under adverse physical circumstances (metabolic or otherwise), which include chromatolysis, retraction, hyperchromasia, nuclear pyknosis, etc. They argue that, on the contrary, psychic stress cannot produce morphological changes in neurons. They cite the example of a curious study comparing the brains of bulls subjected to the stress of a bullfight against the brains of animals killed instantaneously at a slaughterhouse. The analysis by several researchers, blinded to the origin of the brains, identified no differences between the two groups of animals.

6. General staining²³

This chapter, which also lists Escobar as the first author, is shorter, comprising just two pages. This is a choice of the editor, with some idea that is initially unclear, as this is a chapter addressed to general pathologists in a treatise on neuropathology.

The authors begin by noting the existence of a great number of procedures for viewing specific nervous system structures, but at the same time point to the need for general pathologists to know some simple, reproducible techniques for studying the nervous system in everyday practice.

Escobar and Nieto recommend the use of basic haematoxylin-eosin staining, which is able to show the majority of basic changes in neurons, glia, vessels, and neuropil. They suggest adding the following techniques: a stain for elastic arterial fibres, the Nissl method (cresyl violet) for neurons, luxol fast blue (Klüver-Barrera variant) for myelin, the Marchi method for myelin degeneration products, and the Holzer and Mallory methods (phosphotungstic acid haematoxylin) for gliosis.

Discussion

Firstly, we may make some general comments. Without a doubt, it is highly significant that the editors of the first great English-language treatise on neuropathology should commission no fewer than six chapters from Dionisio Nieto and his disciple Alfonso Escobar. For two of these chapters, those dedicated to neurosyphilis and to parasitic diseases, these authors were an obvious choice, given their extraordinary personal experience in both fields. The chapter on cysticercosis shows a remarkable completeness in its descriptions and imagery. Nieto did not take a purely neuropathological interest in cysticercosis^{25,26}; rather, true to his calling as a laboratory man and a promoter of research methods, he also developed serological tests for its diagnosis in living patients.^{27,28}

The most relevant chapters, due to their treatment of longstanding, controversial, and unresolved questions in neuropathology, are those dedicated to epilepsy and psychoses. The fact that they were entrusted to Dr Nieto demonstrates the great recognition and prestige he enjoyed in the field of neuropathology internationally, partly due to his previous publication of original findings on both subjects. Another two chapters, those on stress and general staining, could almost have been hand-picked by the editor for Escobar, who had sufficient expertise to develop both subjects; no further comment will be made on these chapters. It is curious that a chapter on general staining should be entrusted to disciples of the Spanish school of neurohistology, which had developed the main specific stains for each element of the central nervous system, particularly the glia. We should also point out the intellectual honesty of Escobar and Nieto, who did not fall into chauvinism, proposing the use of their school's original stains for general staining, aware of the complexity of these methods and their indication in special circumstances only.

Let us now address certain points in greater depth. The chapter on neurosyphilis reflects once again the enormous importance of the neuropathological study of GPI in the history of psychiatry. This was the first psychiatric entity to be shown to have an organic cause, and therefore attracted great interest from all the neuropathologists of the day, who sought to identify the histopathological basis of other mental illnesses, as explained by Nissl, the mentor of Alzheimer.²⁹ The aim of this tireless

search within these morphological foundations was to identify a neuronal change specific to each entity, similar to neurofibrillary degeneration (tangles) in Alzheimer disease or spherical argyrophilic inclusion bodies in Pick disease. In this chapter, Nieto reviews all the unsuccessful attempts to identify a neuronal lesion specific to GPI, highlighting all the other alterations resembling those of chronic meningoencephalitis, and particularly the intense glial and microglial proliferation. Supported by his extensive experience, he allowed himself to question the value of some of the changes described by the great masters, whom he also honours (eg, Nissl, Alzheimer, and Dejerine), considering these alterations to be non-specific.

A curious experiment that demonstrates Nieto's interest in research is related to the widely recognised but not fully understood preference for lumbar spinal lesions in *tabes dorsalis*. In the years when that disease was common, he used a dark field condenser to demonstrate the presence of spirochaetes in concentrated CSF samples obtained by lumbar puncture. This led him to speculate about the reason for the lesion preference in *tabes dorsalis*.

Nieto's most original contribution in the chapter on neurosyphilis, revealing his interest in methodological developments (doubtless inherited from his master Del Río Hortega), was his novel method for staining spirochaetes. The relationship between GPI and syphilis had already been established in epidemiological and serology studies (Wassermann reaction), but the final endorsement came from Noguchi and Moore,³⁰ who demonstrated the presence of spirochaetes in patient brains. However, their method had the limitation of requiring silver impregnation of the entire block of tissue, which could not subsequently be studied with other techniques. Nieto developed a stain based on uranyl nitrate with silver impregnation, which he performed in individual sections, without spoiling the rest of the tissue block.⁶ Overall, the chapter on syphilis is no less worthy than that written by Greenfield for his celebrated treatise in terms of its content,³¹ and largely surpasses it in terms of the illustrations.

In the chapter on epilepsy, he distinguishes between types of epilepsy: on the one hand, symptomatic epilepsy may be secondary to any cerebral insult, and is given no further attention due to the lack of specificity of these lesions; on the other hand, he considers idiopathic and

temporal lobe epilepsy. These were the three categories recognised in neuropathological texts at the time.³² He highlights the frequent detection of hippocampal sclerosis in both idiopathic and temporal lobe epilepsy. At that time, the concept of idiopathic epilepsy was closer to the modern concept of cryptogenic epilepsy than today's understanding of the former term, which refers more to a genetic aetiology without structural alterations. Appropriately, he cites Spielmeyer, who had observed hippocampal sclerosis in patients with epilepsy secondary to other causes. This leads Nieto to consider that hippocampal sclerosis may be secondary to anoxia or ischaemia.

He contributes no novel details to the description of hippocampal sclerosis itself, but expresses his surprise at the lack of interest to date in the study of potential lesions to structures anatomically related to the hippocampus, known as secondary degeneration. In this regard, he describes atrophy of the fornix, mammillary body, mammillothalamic tract, anterior nucleus of the thalamus, and other structures surrounding the third ventricle, which display demyelination (Figure 3). With Hortega's method, he demonstrates gliosis of the anterior and medial dorsal nuclei of the thalamus (Figure 3). In Nieto's opinion, these changes correspond to degeneration secondary to the primary hippocampal pathology, and it is unlikely that they should be simultaneous lesions with a common cause. Unfortunately, he does not provide details of the number of brains of patients with epilepsy and hippocampal sclerosis he had studied, nor of their characteristics.

It is noteworthy that these findings of Nieto and Escobar²⁰ were unknown at the time, and for many years thereafter. The extraordinary contribution of Falconer³³⁻³⁵ to epilepsy surgery with "en bloc" resection of the anterior temporal lobe, enabling more complete neuropathological study of the epileptic "focus," brought about a period of "hippocampocentrism"³⁶⁻³⁸ in neuropathological research into temporal lobe epilepsy, overshadowing other potentially associated cortical and subcortical lesions, which could only be identified in post mortem studies.

Thus, the presence of these extrahippocampal lesions, with atrophy of the mammillary bodies, mammillothalamic tract, fornix, and thalamus ipsilateral to hippocampal sclerosis, was rediscovered with the advent of modern neuroimaging,³⁸⁻⁴² which substituted classical neuropathology. This led to new neuropathological studies⁴³

that largely confirmed the findings of Nieto and Escobar. Thalamic pathology is not present in all cases, which may be explained by the heterogeneity of the sample. However, the authors did observe a preference for the medial dorsal nucleus, which presented greater neuron density and greater gliosis, as Nieto had previously reported.

Regarding the neuropathology of psychosis, and specifically schizophrenia, Nieto had previously presented a communication describing his findings: diffuse gliosis in the midbrain and diencephalon (Figure 4) ("Cerebral lesions in schizophrenia. Their neuroanatomical and neurophysiological significance." Congress Report, Vol. 2. Second International Congress for Psychiatry; Siebig, Zurich, 1957). The same descriptions were published later by Nieto and Escobar,²¹ and Nieto repeated them in another article in which he related them to probable dysfunction of dopamine and other neurotransmitters.⁴⁴ In an article summarising and praising Nieto's scientific work, Escobar⁶ takes it as given that his contributions to the field of the neuropathology of schizophrenia "have been extensively confirmed" and had given rise to a cascade of research. Indeed, abundant literature has been published in recent years on neuropathological study findings in schizophrenia.⁴⁵⁻⁶⁵ However, only some of these studies⁴⁶ have identified similar diencephalic/mesencephalic gliosis to that reported by Nieto, whereas other authors reject this hypothesis^{48-50,57} or report disparate findings; no further comment will be made on this matter. In fact, some studies report a reduction in glial cells in various structures; this supports the increasingly widely-held view that schizophrenia, or at least some forms of schizophrenia, is not so much a neurodegenerative process but rather a neurodevelopmental disorder.⁶⁶

We may wonder why Nieto's findings have not been confirmed by other authors. Two immediately obvious explanations are the considerable differences between studies in patient selection and study methodology.

In his original work, Nieto analyses the brains of patients diagnosed with schizophrenia of between six and 20 years' progression; the patients were relatively young (29-56 years), enabling us to rule out, in principle, the possibility that the lesions observed may be related to degenerative processes associated with ageing or vascular pathology. He also rules out the presence of other confounding factors, such as medications, toxic substances, or malnutrition. In all cases, death was due to

acute processes (pneumonia, intestinal obstructions, salmonellosis) that should not affect brain morphology. Therefore, Nieto's study sample does not appear to present any particular selection bias among patients institutionalised due to long history of schizophrenia.

What distinguishes Nieto's study from all the others is the methodology of the neuropathological study. Without a doubt, he would have planned the study in advance, as his peculiar methodology begins with fixation of the brain in a medium that enables subsequent staining with Del Río Hortega's lithium carbonate/silver nitrate method, rather than the ordinary formalin fixation typically used to fix brains and other tissues. The second peculiarity is the slicing of the brain in longitudinal or sagittal sections; this is highly unusual in neuropathology laboratories, where brains are typically sliced in coronal or, less frequently, horizontal sections. The decision to slice the brain sagittally was determined by the objective of the study, which according to Nieto aimed to detect subcortical gliosis, particularly in the area surrounding the third ventricle. He already had experience with this objective from previous studies, such as those into neurosyphilis and epilepsy, in which he had used the same technique, judging from the images from his chapters in Minckler's treatise (Figures 1 and 3).^{18,20} Based on these figures, we may deduce that he had already observed that paraventricular gliosis was harder or impossible to detect with coronal slices, whereas it was clearly visible on sagittal slices. The third step was the use of frozen sections. The fourth step, which Nieto alone used in neuropathological studies of patients with schizophrenia, was Del Río Hortega's silver staining method. This stain, as he himself noted, detects not only glial fibrils but all cell bodies.

Taking into account all these peculiarities of Dr Nieto's method (fixation; sagittal/longitudinal slicing of the brain; frozen sections; and Del Río Hortega lithium carbonate/silver staining), alongside his vast experience, proper consideration should be given to his findings before they can be discarded due to their not having been confirmed with other procedures. In a study using the classic Holzer stain for gliofibrils, Stevens⁴⁶ identified gliosis in the same structures as Nieto. On the other hand, a study by Roberts et al.^{48,49} did not confirm this finding. However, there are significant methodological differences between these studies. These authors used immunohistochemistry techniques to detect glial fibrillary acidic protein (GFAP). However, we currently lack

consensus as to whether both methods return similar results. Furthermore, Roberts' group performed coronal sections of the whole hemisphere, embedded in paraffin, making very thick slices (20 µm), and used automated image analysis. In my humble opinion, it is very plausible that, in such thick histological sections, the non-specific background staining may be so intense as to obscure differences between pathological and control tissues. None of the many more recent neuropathological studies mentioned above has sought to confirm Nieto's findings using a similar, if not the same, methodology. The significance of this gliosis of the midbrain/diencephalon, as Nieto himself commented, was unclear. However, it points to the importance of the thalamus and thalamocortical connections in the pathophysiology of schizophrenia, which continues to be studied and debated today in the fields of neuropathology^{57,60,65,67,68} and neuroimaging.

Conflicts of interest

The author has no conflicts of interest to declare. This study received no public or private financial support.

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